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AUTOIMMUNE DISEASES - II

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

I. INTRODUCTION-An autoimmune inflammatory multisystem disease of the connective tissue type having an unknown etiology. Immunologic aberrations with production of autoantibodies and immune complexes leads to tissue injury

II. EPIDEMIOLOGY

A. Prevalence-15-50/100,000 in U.S.

B. Sex preponderance and age of onset-suggest hormonal influence

1. 10:1 female to male with peak onset in 2nd to 4th decade
2. children-3:1 female to male
3. elderly-2:1 female to male
4. 3:1 black to white

C. Genetics

1. >50% concordance in monozygotic twins
2. 5-12% of relatives of patients with SLE develop SLE
3. associations with several HLA types (e.g. DR2 and DR3) and the C4A null allele-heterogeneity of associations suggest multigene theory for SLE inheritance

III. ETIOLOGY AND PATHOGENESIS

A. Hormonal

1. estrogens confer increased risk
2. androgens confer decreased risk
3. Kleinfelters's syndrome-males with XXY have increased SLE risk

B. Precipitating events

1. UV light
2. infection
3. emotional stress
4. surgery
5. pregnancy, post-partum, and abortion

C. Immunologic

1. B cell hyperactivity with hypergammaglobulinemia
2. autoantibodies present with reactivity to DNA, RNA, or phospholipids, or with the proteins that bind to these molecules.
3. clinical manifestations attributable to activity of antibodies to human antigens or the deposition of immune complexes resulting in complement activation, inflammation, and tissue damage
4. serum complement levels often decreased due to immune-mediated complement consumption
5. an essential role for excessive or poorly controlled activity of helper ($CD4^+$) T cells for activation and differentiation of autoantibody-producing B cells appears to represent final common pathway of a heterogeneous disease.
6. trigger(s) of immune dysregulation in genetically susceptible host remain unknown, but viruses, particularly infectious or endogenous retroviral products, are likely candidates.

D. Autoantibodies
1. mostly of the IgG type, lesser extent of the IgM type and are polyclonal
2. primarily target intranuclear nucleic acids, proteins, and ribonucleoprotein complexes (antinuclear antibodies-ANA)
3. different autoantibodies are associated with different clinical manifestations:
a. anti-dsDNA (60-90%)-associated with nephritis; highly specific for SLE
b. anti-Sm (10-30%)-?association with nephritis and CNS manifestations; highly specific for SLE.
c. anti-cardiolipin (10-30%)-associated with thrombosis, fetal loss, thrombocytopenia; not specific for SLE
d. anti-P (10-15%)-associated with lupus psychosis; highly specific for SLE
e. anti-SS-A (20-60%) and anti-SS-B (15-40%)-associated with subacute cutaneous lupus and congenital heart block; somewhat specific for SLE
f. anti-H2A, H2B-associated with drug-induced lupus
4. A negative ANA makes the diagnosis of SLE highly unlikely.

IV. CLINICOPATHOLOGIC FEATURES
A. General
1. constitutional complaints (malaise, overwhelming fatigue, fever, and weight loss) are common presenting features, but not specific for SLE
2. hallmark of SLE is that almost any organ system may be affected in variable combinations; this vast heterogeneity in clinical presentation requires a clinical index of suspicion followed by laboratory confirmation

B. Skin
1. SLE-specific lesions
a. Acute (50% of patients)
i. elevated malar erythematous rash ("butterfly"rash)
ii. typically induced by exposure to sunlight
iii. duration of days to weeks
iv. typically accompanied by other inflammatory manifestations
v. non-scarring
b. Subacute
i. erythematous papules or plaques with light scales (may mimic psoriasis)
ii. associated with musculoskeletal complaints and serum anti-Ro (SS-A) antibody
iii. occur in sun-exposed areas
iv. non-scarring
c. Chronic (discoid)
i. erythematous papules or plaques with thick scales
ii. scarring with central atrophy
iii. scalp lesions may lead to extensive and permanent alopecia
iv. also occur in sun-exposed regions
v. dermal-epidermal distribution of immune complexes and chronic inflammatory cells
2. Non-specific skin lesions
a. ulcerations of oral mucosa, vagina, and nasal septum
b. alopecia-patchy or diffuse even in absence of chronic discoid lesions
c. vascular lesions
i. Raynaud's (50%)
ii. vasculitis

C. Musculoskeletal
1. Arthralgias and/or arthritis
a. most common presenting manifestation of SLE

b. small joints of hands, wrists, and knees (symmetrical)
c. typically non-erosive (unlike rheumatoid arthritis) but can be deforming
d. mild synovial inflammation

2. Myopathy
a. muscle pain and weakness
b. may be associated with polymyositis or due to corticosteroid use

D. Renal disease
1. recognized by abnormal urinalysis and elevated serum creatinine; clinical manifestations occur only late in the course
2. Glomerular, tubulointerstitial, and vascular lesions secondary to immune complex deposition
3. presence of hematoxylin bodies (pathognomonic)
4. nearly all renal biopsies will show some abnormality; has both prognostic and therapeutic implications and thus may be of importance

E. Neuropsychiatric
1. wide spectrum of clinical findings; more than one pathogenetic mechanism postulated but these are not well-understood
2. Neurologic
a. intractable headaches-most common neurologic feature
b. seizures-focal or generalized
c. cranial or peripheral neuropathy
d. anti-cardiolipin antibody-associated
i. stroke (thrombosis)
ii. chorea (movement disorder)
e. retinopathy-secondary to vasculitis
3. Psychiatric
a. psychosis and severe depression-anti-P antibody
b. organic brain syndrome (state of disturbed mental function)-potential role of anti-neuronal antibodies

F. Serositis
1. pleuritis (30-60%)-pleuritic chest pain, rubs, and effusion
2. pericarditis (20-30%)-precordial chest pain, rubs, and effusion
3. peritonitis (60%)
a. may be cause of "gastrointestinal syndrome"-diffuse abdominal pain, anorexia, nausea, and occasionally vomiting.

G. Pulmonary
1. acute pneumonitis may simulate pneumonia
2. chronic diffuse interstitial lung disease

H. Cardiac
1. myocarditis leading to arrhythmia, conduction defects, cardiomegaly, congestive heart failure, or tachycardia
2. endocarditis
a. non-bacterial verrucous valvular vegetations (Libman-Sacks endocarditis)
b. 15-60% of patients at autopsy
c. valvular replacement required only on occasion

I. Hematologic-pancytopenia, usually mild , secondary to anti-blood-cell antibodies

V. DRUG-INDUCED SLE
A. diagnosis-no prior history of SLE, clinical and serological manifestations of SLE develop while on drug, improvement occurs quickly after stopping drug

B. drugs most strongly implicated-chlorpromazine, methyldopa, hydralazine, procainamide, and isoniazid

C. clinical features less severe than idiopathic SLE

D. most common features-constitutional, fever, arthritis, and serositis

E. positive ANA but anti-dsDNA antibody not found

F. serum complement levels typically normal

VI. TREATMENT

A. therapy for acute flares must be distinguished from long-term management strategies

B. corticosteroids important for serious, acute, active SLE; but NSAID's are the first line of treatment for many manifestations.

C. anti-malarials are effective for skin and other organ involvement

D. renal function is preserved by intravenous cyclophosphamide in patients with nephritis

FREQUENCY OF LUPUS MANIFESTATION			
Manifestations	**At Onset**	**Anytime**	
	(108)	**(605)**	**(520)**
Constitutional	73%	84%	86%
Arthritis	56%	63%	92%
Arthralgia	77%	85%	92%
Skin	57%	81%	72%
Mucous membranes	18%	54%	9%
Pleurisy	23%	37%	45%
Lung	9%	17%	-
Pericarditis	20%	29%	31%
Myocarditis	1%	4%	8%
Raynaud's phenomenon	33%	58%	18%
Thrombophlebitis	2%	8%	-
Vasculitis	10%	37%	21%
Renal	44%	77%	46%
Nephrotic syndrome	5.00%	11%	23%
Azotemia	3%	8%	-
CNS	24.00%	54 %	26%
Cytoid bodies	5.00%	5 %	10%
Gastrointestinal	22%	47%	49%
Pancreatitis	1.00%	4%	-
Lymphadenopathy	25.00%	32%	59.00%
Myositis	7.00%	5.00%	

Figure 11-1. Frequency of lupus manifestations. Frequency of lupus manifestations at onset based on 108 patients diagnosed at the University of Toronto Lupus Clinic and at anytime for 605 patients registered prior to December, 1990 and in 520 patients at the University of Souther California at Los Angeles.

SYSTEMIC SCLEROSIS

Systemic Sclerosis (SS) [Scleroderma]

I. INTRODUCTION: Systemic sclerosis (scleroderma) is a member of the connective tissue disease family having an uncertain etiology and pathogenesis and characterized by evidence of vascular injury and immune cell activation. These events are associated with excessive deposition of collagen in the skin, intimal fibrosis and narrowing of blood vessels leading to ischemia in multiple organs, and vascular instability leading to episodes of vasospasm.

II. EPIDEMIOLOGY:

A. Prevalence-50,000-100,000 cases in U.S.

B. Sex preponderance-3-4 x female > male.

C. Peak age of onset-30-50 y.o.; 3% of cases in children (usually limited form).

D. Genetics

1. familial aggregation is rare; however other autoimmune diseases and anti-nuclear antibodies are common in family members.
2. Gene not identified, however distinct MHC-associated autoantibody responses exist within the affected population which have specific clinical correlates; no gene outside the MHC has been linked to susceptibility.

III. ETIOLOGY AND PATHOGENESIS:

A. Inciting event unknown, but believed to involve an environmental stimulus interacting with a genetically predisposed individual.

B. Proposed pathogenetic mechanism:

1. vascular injury of an ill-defined nature is associated with immune cell activation; adhesion molecules are induced on endothelial cells.
2. adhesion to endothelial cells and transmigration of T cells and monocytes occurs with release of cytokines.
3. cytokine activation of fibroblasts and smooth muscle cells results in fibrotic tissue deposition in arterial walls, dermis of skin, and certain internal organs.
4. elevated tissue levels of TGF-$ suggests a role in enhanced fibrogenesis.
5. Animal model-The tsk ("tight skin") mouse-dermal thickening although no vascular changes.

C. Autoantibody production

1. Systemic sclerosis is a serologically heterogeneous disorder. MHC class II associations are less with systemic sclerosis per se but are instead with autoantibody subsets.
2. Autoantibodies vary in frequency between different ethnic and racial groups and are associated with important clinical manifestations.
3. Anti-centromere antibodies
   a. predominantly in Caucasians
   b. associated with CREST syndrome (limited SS)
4. Anti-topoisomerase antibodies
   a. associated with pulmonary fibrosis and diffuse skin involvement.
5. Anti-nucleolar antibodies
   a. anti-PM-Scl -in Caucasians and associated with inflammatory myopathy.
   b. anti-fibrillarin-higher frequency in African-Americans and men and associated with diffuse skin involvement and pulmonary hypertension.

IV. CLINICOPATHOLOGIC FEATURES:

A. natural course may vary widely; majority undergo progression of skin and internal organ involvement with considerable morbidity and mortality; cumulative survival rate of 30% at 12 years.

B. internal organ involvement, presence of anti-topoisomerase antibodies and diffuse skin involvement adversely affect outcome.

C. Subtypes:

1. Limited (CREST syndrome)-calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangectasia); skin and organ involvement limited.
2. Diffuse-involvement of skin areas proximal to the elbow and knee correlates with an increased probability for severe organ dysfunction and decreased survival.

D. Skin involvement

1. early phase (inflammatory)-excessive deposits of "young" collagen (types I and III), matrix components, edema, and inflammatory infiltrates (monocytes and CD4+ T cells); peaks at 2-3 years (thus if involvement is going to be severe it occurs during this 2-3 year period).
2. late phase (fibrosis and atrophy)-inflammatory infiltrates disappear, dermis replaced by lesser amounts of denser collagen, loss of skin appendages and epidermal atrophy.
3. first signs of skin involvement usually appear as swelling and puffiness, especially of fingers and hands with progression to other areas of skin.

E. Vascular Involvement

1. Raynaud's phenomenon
   a. vasospasm of digital arteries induced by cold or emotional stress; color progression from white (vasospasm) to blue (cyanosis) to red (compensatory vasodilation).
   b. initial complaint in 70%; nearly all eventually develop; however not specific for SS; .
   c. diagnosis largely based on clinical criteria.
   d. evidence for complex functional vascular disorder involving interactions between endothelial cell products (i.e. endothelin [a vasoconstrictor] and endothelial-dependent relaxation factor [EDRF]), platelet-released products, and neuropeptides.
   e. leads to digital necrosis.
2. Small arteries and arterioles
   a. intimal fibrosis and luminal narrowing with ischemia and eventual atrophy and dysfunction of dependent tissue.
3. Microvasculature
   a. characteristic vascular pattern by nailfold capillaroscopy best non-invasive test to demonstrate microvascular derangement in SS.
   b. decrease in total number of capillary loops and increased numbers of wide and giant loops.

F. Renal

1. Scleroderma renal crisis
   a. occurs in ~10% of patients
   b. hyper-reninemia, malignant hypertension and rapid development of renal insufficiency.
   c. interlobular and arcuate arteries involved

d. once a major cause of death; now can be successfully treated with angiotensin converting enzyme (ACE) inhibitors in majority of patients.

G. Pulmonary

1. pulmonary manifestations in 60-80% of patients; leading cause of mortality;
2. Progressive interstitial fibrosis
    a. when significant fibrosis occurs it appears early and is accompanied by inflammatory infiltrates (neutrophils and $CD8^+$ T cells)
    b. most rapid decline in lung function occurs within first 4 years;
    c. fibrosis once established is irreversible.
3. Progressive pulmonary hypertension
    a. can occur independent of pulmonary fibrosis and tends to appear late in disease course.
    b. once present it progresses rapidly; death within 2-3 years of onset.

H. Gastrointestinal

1. second most common affected organ after the skin; GI manifestations in ~80% of patients with SS; rarely results in mortality.
2. main clinical manifestations
    a. gastroesophageal reflux
    b. dysphagia and odynophagia
    c. malabsorption
    d. intestinal pseudoobstruction
    e. small bowel bacterial overgrowth
3. pathogenesis (in order of development)
    a. neural dysfunction
    b. smooth muscle atrophy
    c. muscle fibrosis

I. Malignancy

1. increased risk of cancer associated with patients with older age at diagnosis and presence of anti-topoisomerase I antibodies.

J. Treatment

1. currently no accepted specific treatment that alters course of disease.
2. results of traditional immunosuppressive regimens for autoimmune disease generally disappointing.
3. expanded knowledge of pathogenesis in recent years forms basis for testing multiple new therapeutic strategies.